REMARKS

I. Status of the claims

Claims 1, 2, 6-9, 13, 14, 16-20, 24-28 are pending. The Examiner has withdrawn from consideration claims 26-29, contending that they are drawn to an "independent or distinct" invention. Office Action at page 2. Since Applicants have incorporated the subject matter of claim 29 into claim 1, they have canceled claim 29 without prejudice or disclaimer. Applicants also have canceled claims 22 and 23, which recited the Röhm GmbH & Co. KG "Eudragit® E" trademark. Accordingly, the Examiner's rejection of claims 22 and 23 at page 3 of the Office Action is moot.

All of the pending claims have been amended to ensure correct antecedent basis for the "medicinal powder" of claim 1, instead of the originally recited "preparation." Claims 7, 9, 13, 16, 17, and 25 have been amended so that they no longer recite a "high molecular weight" and so that they agree with the language used to qualify the medicine of claim 1. Claim 1 has been amended for the reasons that follow.

(a) Amendment to claim 1 clarifies the claimed powder as an "admixture" of medicine and cationic aminoalkylmethacrylate copolymer

Applicants have amended claim 1 to better clarify the claimed powder as an "admixture" of (i) a medicine that has a molecular weight greater than 1000 and (ii) a cationic aminoalkylmethacrylate copolymer. The specification is clear that the medicine and copolymer are mixed together in powder form. See, for instance, page 5, lines 17-21, which describes "a pharmaceutical composition in powder form, comprising a medicine of high molecular weight and a cationic polymer." Similarly, Example 3, 4, 5, 6, 7, 8, 9, and 10 of the present application disclose a spray-dried, powdered "mixture" of, for instance, G-CSF and "copolymer E (Eudragit® E100)" for pernasal administration. Accordingly, denoting the powder of claim 1 as an "admixture" of medicine and methacrylate copolymer adds no new matter to claim 1 and Applicants respectfully request that the Examiner enter this amendment.

In this respect, Applicants thank Examiner Gollamudi for extending the courtesy of a teleconference with Applicants' representatives on May 12, 2004, where she agreed that such an amendment to claim 1 is appropriate. Examiner Gollamudi also indicated that she may find the recited "admixture" to structurally distinguish the claimed powder over Norling *et al.* (U.S. Patent No. 5,958,458) as Applicants contend below.

II. Cumming et al. (U.S. Patent No. 6,153,220) does not teach an admixture of cationic aminoalkylmethacrylate copolymer and a medicine that has a molecular weight greater than 1000 as presently recited

The Examiner rejected claims 1, 7, 9, 13-14, 16-17, 19-20, and 22-25 as allegedly unpatentable over Cumming *et al.* (U.S. Patent No. 6,153,220) under 35 U.S.C. § 103(a).

(a) Cumming does not teach a medicine that has a molecular weight greater than 1000 MW

Applicants have amended claim 1 to qualify the "high" molecular weight medicine as one that has a molecular weight "greater than 1000 MW." Exemplary support for this qualification can be found at page 2 of the specification. Cumming does not teach a powder that comprises a medicine that has a molecular weight greater than 1000 MW.

In this respect, Applicants reiterate that Cumming's exemplified drugs (at column 3, lines 5-26) are *low* molecular weight drugs that have a smaller molecular weight than the minimal molecular weight presently recited. For example, a random selection of those exemplified drugs indicates that "prostaglandin" has a molecular weight of 352 MW; "ampicillin" has a molecular weight of 349.41 MW; "prednisolone" has a molecular weight of 360.45 MW; "ketoprofen" has a molecular weight of 254.29 MW; "acetaminophen" has a molecular weight of 151.16 MW; "ibuprofen" has a molecular weight of 206.28 MW; "naproxen" has a molecular weight of 230.26 MW; "acetylsalicylic acid" has a molecular weight of 180.16 MW; and "caffeine" has a molecular weight of 194.19 MW. Also, the "Nizatidine" drug in Cumming's Example 1 has a molecular weight of 331.47 MW (column 3, lines 64).

The Examiner contends that Cumming's "disclosed examples, *i.e.* the use of low molecular drugs, do not constitute a teaching away from the broader disclosure, *i.e.* the use of

proteins, peptides, *etc.*" Office Action at page 6. However, there is nothing in Cumming to suggest that a >1000 MW protein, which has poor organoleptic properties, can be treated in the same fashion as the forty-nine low molecular weight "typical drugs" exemplified at column 3, lines 13-27 of Cumming.

(b) Cumming is not analogous art because it describes how to mask the bitter taste of low molecular weight drugs, whilst the present invention discloses a composition and method for improving the adsorption of a medicine greater than 1000 MW across a mucosal membrane

Cumming is not analogous art. In rejecting a claim under 35 U.S.C. § 103, the Examiner must determine what is "analogous prior art" for the purpose of analyzing the obviousness of the subject matter at issue. "*In order to rely on a reference as a basis for rejection of an applicant's invention, the reference* ***must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned***" (emphasis added; *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445, Fed. Cir. 1992). MPEP, Section 2141.01(a).

Cumming is not in the field of Applicants' endeavor and it certainly is not "reasonably pertinent" to the particular problem addressed by the present application. Cumming in no way addresses the problem of improving the absorption of a medicine greater than 1000 MW across a mucosal membrane. Cumming teaches only "the advantageous use of employing cationic copolymers ... to provide adequate elimination of the unpleasant organoleptic properties of the drug" (column 1, line 64 to column 2, line 9).

Therefore, the person, who would have turned to Cumming for drug-formulation guidance, would have been one skilled in the art of "taste-masking," not one skilled in the art of enhanced mucosal adsorption of a high molecular weight medicine. Accordingly, the person skilled in the art of "taste-masking" would have appreciated that the range of drugs exemplified by Cumming indeed are "typical" of the low molecular weight compounds in need of flavor enhancement. Certainly, the person skilled in that art was well aware that the majority of the "taste-masking" literature dealt with the disguising of bitter tasting small peptides. Accordingly, he would have identified in Cumming only an allegedly new method for masking such already-known small, low molecular weight compounds and peptides. He

would have found nothing in Cumming to suggest a taste-masking protocol for disguising the taste of a medicine larger than 1000 MW. Accordingly, the skilled person would *not* have been "motivated to utilize a particular drug depending on the symptom to be treated" as the Examiner contends (Office Action at page 5).

Thus, the person of ordinary skill would have found no motivation to formulate a >1000 MW drug that has poor organoleptic properties, with a cationic methacrylate copolymer as taught by Cumming. Accordingly, claims 1, 7, 9, 13-14, 16-17, 19-20, and 22-25 are not rendered obvious by Cumming *et al.* For at least the reasons presented herein, Applicants respectfully request that the Examiner withdraw this rejection.

III. Norling et al. (U.S. Patent No. 5,958,458) does not teach an admixture of cationic aminoalkylmethacrylate copolymer and a medicine that has a molecular weight greater than 1000 as presently recited

The Examiner rejected claims 1-2, 6-9, 13-14, 16-20, and 22-25 as allegedly unpatentable over Norling *et al.* (U.S. Patent No. 5,958,458) under 35 U.S.C. § 103(a). The Examiner was unpersuaded by Applicants' arguments of December 4, 2003, and stated that "'consisting essentially language' only excludes components that affect the basic composition . . . inert materials [such as Norling's "inert core"] do not change the basic property of a product since it has no affect on the composition" (Office Action at pages 7 and 8).

The Examiner considered Dr. Nomura's Declaration of June 20, 2003, to fail to relate any unexpected results because "unexpected results should be compared to the closest prior art, *i.e.*, Norling's composition to instant composition." Office Action at page 8.

(a) It would have been nonsensical to perform an experimental comparison of Norling against the presently claimed powdered admixture because the two compositions are not equivalent and are formulated for different purposes

Norling's composition is structurally distinct from the presently claimed powder. Norling's composition is a rigid, structured pellet, which layers Eudragit E as a discrete film coating onto that pellet. On the other hand, the composition of present claim 1 is a powdered admixture of a methacrylate copolymer and a medicine larger than 1000 MW in molecular weight. Norling's composition was formulated according to traditional tablet formulation

strategies. Applicants, however, conceived of an admixture of a cationic aminoalkylmethacrylate copolymer and a medicine, where the presence of the copolymer actually enhances the absorption of the medicine across a mucosal membrane. Thus, it would have made no sense to compare the presently claimed powder against Norling's composition because the two compositions are not equivalent and are formulated for different purposes.

(b) The claimed powder is an intimate admixture of (i) a medicine that has a molecular weight greater than 1000 and (ii) an aminoalkylmethacrylate copolymer, whilst Norling's composition is a pelleted, structured drug core coated with a layer of acrylate

The powder of present claim 1 is an intimate admixture of a medicine that has a molecular weight greater than 1000 and an aminoalkylmethacrylate copolymer. Applicants unexpectedly discovered that the presence of the cationic copolymer, intermixed with the medicine, enhances the transmission of the medicine across the mucosal membrane. This result is very likely due to the fact that the mucosal membrane is *simultaneously* exposed to the medicine and methacrylate and, therefore, subjected to their respective activities concurrently. By contrast, the respective activities of the coating and the drug in Norling's formulation are temporally and functionally *disconnected* and distinct. One obvious reason for this disconnect is that the methacrylate copolymer, Eudragit® E, when used to coat Norling's pellet, is gastrosoluble and disintegrates away from the pellet after administration.

Applicants provide herewith a Rule 1.132 Declaration executed by Dr. Nomura, a co-inventor of the present application, attesting that the two compositions are not equivalent. Norling's pellets comprise solid inert carrier "cores" that are layered with an active substance (column 2, lines 10-21), and then coated with a protective or release-modifying film. Without the solid core, Norling informs that it would be difficult, if not impossible, for the pellets to withstand the coating process (column 2, lines 33-39). Appended to Dr. Nomura's declaration as Exhibit A is a schematic diagram illustrating the differences in structure between Norling's composition and the powder of claim 1.

(c) Norling's method of making the prior art composition does not require mixing together a medicine and a methacrylate copolymer and, therefore, the resultant composition is structurally and functionally distinct from the presently claimed powder

To appreciate the structural distinctions between Norling's composition and the powder of present claim 1, it is helpful to understand how both compositions are made. In Norling's case, a suspension of active ingredient and inert carrier is produced that is then spray-dried to form inert core pellets (Example 3, column 26, lines 8-67). A *film coating* of Eudragit® (specifically Eudragit® RS) solution is then applied to the core pellets (Example 10, column 32, lines 13-66), which are subsequently directly compressed into a tablet (Example 12, column 35, line 34 to column 36, line 30).

According to Norling, the methacrylate coating provides "the desired release profile of the active substance included in the cores, or alternatively mask the taste of the bad-tasting active substances . . . the cores may contain two or more *layers* of coating" (emphasis added; column 8, lines 43-50). Norling in no way teaches that the film coating material can be used for a purpose other than as a veneer over the drug-carrier core. For instance, Norling does not suggest filling the core with inert carrier, active substance, *and* Eudragit®. To have done so would have been nonsensical, since Norling teaches the film coating is used to protect the pre-formed, solid drug cores prior to tablet formation and administration.

By contrast, Applicants' method for making the presently recited powder precisely requires that mixture. Applicants' method requires (i) mixing a solution of cationic aminoalkylmethacrylate copolymer directly with a buffer solution of a desired medicine, and then (ii) spray-drying the resultant liquid to produce a powder for pernasal administration. See Examples 3 to 10 at pages 16 to 19 of the present specification. Hence, the *admixed* powder composition of claim 1 is structurally and functionally distinct from Norling's "multiple unit particulate" formulation.

For at least these reasons, Applicants contend that claims 1-2, 6-9, 13-14, 16-20, and 22-25 are patentable over Norling, and respectfully request that the Examiner withdraw this rejection.

IV. Claim 8 is not unpatentable over Norling et al. (U.S. Patent No. 5,958,458)in view of JP 406065090 because no combination of the references teaches an admixture of cationic aminoalkylmethacrylate copolymer and a medicine that has a molecular weight greater than 1000 as presently recited

The Examiner rejected claim 8 under 35 U.S.C. § 103(a) as allegedly unpatentable over Norling *et al.* in view of JP 406065090, because the Japanese reference teaches the subject matter of claim 8, namely G-CSF.

Since no combination of the two references teach each and every limitation of the presently claimed invention, as detailed for Norling in the preceding section III, claim 8 is not rendered obvious. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

V. Claim 18 is not unpatentable over Norling et al. (U.S. Patent No. 5,958,458)in view of Stanton et al., (U.S. Patent No. 5,807,552) because no combination of the references teaches an admixture of cationic aminoalkylmethacrylate copolymer and a medicine that has a molecular weight greater than 1000 as presently recited

The Examiner rejected claim 18 under 35 U.S.C. § 103(a) as allegedly unpatentable over Norling *et al.* in view of Stanton *et al.*, (U.S. Patent No. 5,807,552), because the Stanton teaches the subject matter of claim 18, namely a hapten-carrier.

Since no combination of the two references teach each and every limitation of the presently claimed invention, as detailed for Norling in the preceding section III, claim 18 is not rendered obvious. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

VI. Conclusion

Applicants believe that the present application now is in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 2 July 2004 By S. A. Bent

FOLEY & LARDNER
Customer No. 22428
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768